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ANTONELLI, TERRY, STOUT & KRAUS, LLP
1300 NORTH SEVENTEENTH STREET
SUITE 1800
ARLINGTON, VA 22209-3873

EXAMINER	
BHAT, NARAYAN KAMESHWAR	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,747	KOBAYASHI ET AL.	
	Examiner	Art Unit	
	NARAYAN K. BHAT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19 and 21-28* is/are pending in the application.

4a) Of the above claim(s) *8-16 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7, 17, 19 and 21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL ACTION

1. This office action is written in reply to Applicant's correspondence filed January 29, 2009. Applicant's amendment requiring visualizing and identifying an individual chain molecule immobilized on a plastic substrate and as immobilized being uprightly disposed relative to said plastic substrate necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.**

Status of the Claims

2. This action is in response to papers filed on January 29, 2009, wherein claims 1and 19 have been amended. New claims 27 and 28 are added. Claim amendments are reviewed and entered.

3. The previous rejections under 35 USC § 102 (b) and 103(a) are withdrawn in view of amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections.

4. Claims 8-16 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement made final on June 12, 2007.

5. Claims 1-19 and 21-26 are pending in this application.

6. Claims 1-7, 17, 19 and 21-28 are under examination.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-5, 17, 19, 21, 22 and 25-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liu et al (Nano Letters, 2002, 2, 863-867) in view of Obremski et al (USPGPUB NO. 2002/0001853 published Jan. 3, 2002) and further in view of Seong et al (Anal. Chem. 2000, 72, 1288-1293).

Regarding claim 1, Liu et al teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and as immobilized being uprightly disposed relative to said substrate (Fig. 1, pg. 865, column 1, paragraph 1) by probing with scanning probe microscope in solution (Abstract, Figs. 3A and 4A, pg. 865, column 2,

paragraph 2). Liu et al do not teach about plastic substrate and visualizing and identifying an individual chain molecule.

Regarding claim 2, Liu et al teaches that chain molecule (i.e., single stranded DNA) is immobilized on the gold surface (Fig. 2C, pg. 864, column 1, and last paragraph) and is an uprightly disposed single stranded DNA molecule (i.e., stand up configuration, pg.865, column 1, paragraph 1).

Regarding claim 3, Liu et al teaches that the uprightly single strand molecule is a nucleic acid (Fig. 1, pg. 865, column 1, and paragraph 1).

Regarding claim 4, Liu et al teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 5, Liu et al teaches that the multiple strand molecules are a complex of single strand DNA and protein DNaseI (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claim 17, Liu et al teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claim 19, Liu et al teaches a molecular detection method comprising visualizing and identifying chain molecule (Figs. 4A and 4G, pg. 865, column 2, paragraph 3) immobilized on a substrate and as immobilized being uprightly disposed relative to said substrate (Fig. 1, pg. 865, column 1, paragraph 1) by probing with

scanning probe microscope in solution (Abstract, Figs. 3A and 4A, pg. 865, column 2, paragraph 2), wherein the molecule immobilized on the substrate is a nucleic acid (Fig. 2, pg. 864, column 1, paragraph 3). Liu et al do not teach about plastic substrate and visualizing and identifying an individual chain molecule.

Regarding claim 21, Liu et al teaches that the chain molecule is in stand up position (Fig. 1, pg. 865, column 1, paragraph 1) and the binding of DNase I molecule to the uprightly disposed chain molecule comprises multi-strand molecule.

Regarding claim 22, Liu et al teaches that the multiple strand molecules are a complex of single strand DNA and protein DNaseI (pg. 865, column 2, paragraphs 2 and 3, pg. 866, column 1, paragraph 1).

Regarding claim 25, Liu et al teaches a production process for immobilizing the single stranded DNA, i.e., chain molecule on a substrate (Fig. 2, substrate – labeled as Au (III), pg. 864, column 1, paragraph 4) and further teaches that the immobilized single strand DNA is in uprightly disposed position (Fig. 1, pg. 865, column 1, paragraph 1).

Regarding claim 26, Liu et al teaches the substrate is gold (Fig. 2, pg. 864, column 1, last paragraph), but do not teach about plastic surface.

Regarding claims 27 and 28, Liu et al teaches that the molecule, as immobilized, is uprightly disposed relative to the substrate so as to extend substantially perpendicularly from said substrate (Figs. 1 and 3A, pg. 865, column 1, paragraph 1, lines 2-4)).

Regarding claims 1, 19 and 26, Liu et al do not teach about plastic substrate. However, a plastic substrate for immobilizing chain molecules were known in the art at

the time of the claimed invention was made as taught by Obremski et al who teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski et al also teaches molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski et al also teaches that plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation method molecular detection (paragraphs 0038 and 0071).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the substrate of Liu et al with plastic substrate of Obremski et al with a reasonable expectation of success.

An artisan would have been motivated to modify the substrate of Liu et al with the expected benefit of having a plastic surface, that is optically transparent, having a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation molecular detection as taught by Obremski (paragraphs 0038 and 0071).

Regarding claims 1 and 19, Liu et al teaches the visualizing and identifying about 26 molecules in an 80.5 nm2 area (Fig. 3E, lane a2, area indicated by an arrow, pg. 865, column 1, paragraph 2). Obremski et al also teaches an AFM scanning of immobilized avidin array and further teaches that avidin extends 200 nm vertically from the surface and binds to biotin (paragraph 0071). Liu et al and Obremski et al do not teach about visualizing and identifying an individual chain molecule by scanning probe

microscope in solution. However, visualizing and identifying an individual chain molecule by scanning probe microscope in solution was known in the art at the time of the claimed invention was made as taught by Seong et al.

Seong et al teaches visualization and identification of RecA protein binding to the single stranded DNA by scanning the complex by AFM in solution (Abstract, pg. 1288, column 1, and paragraph 1). Seong et al also teaches visualization and identification of single chain molecule (i.e., target DNA, Abstract). Combined teachings of Liu et al, Obremski et al and Seong et al, thus would provide a method of visualizing and identifying a single strand DNA individual chain molecule uprightly immobilized on a plastic substrate by probing with an AFM scanning probe microscope in solution.

Seong et al also teaches that the AFM imaging allows to study small proteins binding to their individual target sequences under native conditions and for gene mapping on individual double stranded DNA for further enhancing the understanding of macromolecular interactions responsible for genetic and cellular regulation (pg. 1289, column 1, paragraphs 1 and 2).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the molecular detection method of Liu et al with the method of visualizing and identifying individual chain molecule of Seong et al with a reasonable expectation of success.

An artisan would have been motivated to modify the molecular detection method of Liu et al with the expected benefit of studying small proteins binding to their individual target sequences under native conditions and for gene mapping on individual double

stranded DNA for further enhancing the understanding of macromolecular interactions responsible for genetic and cellular regulation as taught by Seong et al (pg. 1289, column 1, paragraphs 1 and 2).

10. Claims 1-3, 6-7, 19, 23-24 and 27-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (USPN 7,033,476 filed Dec. 31, 2002) in view of Obremski et al (USPGPUB NO. 2002/0001853 published Jan. 3, 2002).

Regarding claims 1, 19 and 27-28, Lee et al teaches a molecular detection method comprising visualizing and identifying single molecules by probing with scanning probe microscope in solution (Fig. 5, Scanning probe, # 78, column 5, lines 40-52). Lee et al further teaches that a nanogate is formed on the substrate (Fig. 4, Substrate # 40, nanogate # 42) and nucleic acid sample molecules are held at the gate by perpendicular electric field (Fig. 4, column 4, line 60, column 5, lines 53-58, column 8, lines 43-67), thus teaching single molecules are immobilized on a substrate and as immobilized being uprightly disposed relative to the substrate. Lee et al do not teach about plastic substrate.

Regarding claims 2 and 3, Lee et al teaches that single strand molecule is a protein (column 5, line 28).

Regarding claims 6, 7, 23 and 24, Lee et al teaches detecting and counting single molecule immobilized within the nanogate (column 8, lines 43-67) thus teaching number of detected molecules per unit area, thus giving the molecular localization information.

Lee et al do not teach about plastic substrate. However, a plastic substrate for immobilizing chain molecules were known in the art at the time of the claimed invention was made as taught by Obremski et al who teaches an assay method comprising a plastic substrate (paragraph 0038) for immobilizing oligonucleotide probe (paragraph 0010). Obremski et al also teaches molecules immobilized on the plastic substrate stand up "vertically" from the surface (paragraph 0071). Obremski et al also teaches that plastic surface is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation method molecular detection (paragraphs 0038 and 0071).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the molecular detection method of Lee et al with the plastic surface of Obremski et al with a reasonable expectation of success.

An artisan would have been motivated to modify the molecular detection method of Lee et al with the expected benefit of having a plastic surface, that is optically transparent, has a higher refractive index than water, easy to configure to different dimensions and amenable for chemical coupling and is well suited for AFM and evanescent wave excitation molecular detection as taught by Obremski (paragraphs 0038 and 0071).

Response to remarks from the Applicants

Claim rejections under 35 U.S.C. § 103(a)

11. Applicant's arguments filed on January 29, 2009 with respect to claims 1-5, 17, 19, 21-22 and 25-26 being unpatentable over Liu et al, Obremski et al and Seong et al (remarks, pgs. 8-15) and with respect to claims 1-3, 6-7 and19, 23-24 (Remarks, pgs. 15-17) have been fully considered but are not persuasive for the following reasons.

Applicant's arguments are directed towards cited art not disclosing or suggesting a molecular detection method as recited in instant claims in particular individual chain molecules are immobilized on a substrate in uprightly disposed relative to the substrate and visualizing and identifying the said molecules by scanning probe microscope in solution. This argument is not persuasive because as described above in section 9, Liu et al teaches single stranded DNA molecule immobilized on a substrate in uprightly disposed relative to the substrate and visualizing and identifying the said molecules by scanning probe microscope in solution (Fig. 1 and 3A).

Also, Liu et al teaches that the single stranded DNA molecules are attached to the substrate surface from one end using a thiolated linker so that the single stranded molecules are immobilized in a vertical position relative tot the substrate. Furthermore, Applicants have asserted that Liu et al teaches visualizing and identifying the aggregates of the thiolated DNA molecules (Remarks, pg. 13, paragraph 1), i.e., aggregate of the individual thiolated DNA molecules. Also, Obremski et al also teaches the chain molecules are immobilized vertically relative to the substrate (paragraph 0071). Seong et al is relied upon for individual molecule analysis. It is maintained that

Liu et al, Obremski et al and Seong et al teaches visualizing and identifying an individual chain molecules immobilized on a substrate in uprightly disposed relative to the plastic substrate by probing with scanning probe microscope in solution. Therefore, arguments are not persuasive.

Applicants further argue that Liu et al neither discloses nor suggests molecular detection method as in the instant claims (Remarks, pg. 12, paragraph 2). This argument is not persuasive for the same reasons as described above.

Applicants further argue that "Liu et al teaches visualizing and identifying the aggregate" (Remarks, pg. 14, paragraph 1). This argument is not persuasive because as discussed above, Liu et al teaches that the single stranded DNA immobilized on the surface are uprightly disposed single stranded DNA. Furthermore, Seong is relied upon for individual molecule analysis.

Applicants further argue that even if the teachings of Obremski et al are combined with the teachings of Liu et al, such teachings would have neither disclosed or would have suggested the presently claimed invention (Remarks, pg. 14, paragraph 1). This argument is not persuasive for the same reasons as described above.

Applicants further reiterate that Seong et al teaches that the DNA-protein complexes absorbed parallel to the mica surface and therefore one having the ordinary skill in the art would not have combined the teachings of Seong et al and Liu et al (Remarks, pg. 15, paragraph 1). This argument is not persuasive because as described above, Liu et al and Obremski et al teaches immobilization of molecules uprightly disposed relative to the plastic substrate and Seong et al are relied upon for individual

molecule analysis. Furthermore, Applicants have not provided support documents or affidavits in support of their arguments, why teachings of Seong et al of individual molecule analysis won't work in the method of Liu et al. It is maintained that Liu et al, Obremski et al and Seong et al teaches a method as claimed. Therefore, arguments are not persuasive.

Applicants further argue that Lee et al neither disclose or suggest the claimed molecular detection method and teach away from the claimed method (Remarks, pg. 16, paragraph 2). This argument is not persuasive because as described above in section 10, Lee et al teaches single nucleic acid molecules are held at the nanogate by perpendicular electric field, i.e., molecules are uprightly disposed relative to the substrate as claimed and molecules are visualized, identified and counted at the gate by scanning probe microscope in solution. Furthermore, Applicants have not provided support documents or affidavits in support of their arguments, why teachings of Obremski et al of plastic substrate in place of substrate of Lee et al won't work.

Also, courts have ruled that Applicant's arguments by attacking references individually are not persuasive wherein the rejections are based on combinations of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)).

Furthermore, arguments of counsel are not found persuasive in the absence of factual showing. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and

which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

In the instant case, Lee et al and Obremski et al teach visualizing and identifying an individual chain molecules immobilized on a substrate in uprightly disposed relative to the plastic substrate by probing with scanning probe microscope in solution. Therefore, arguments are not persuasive.

Conclusion

12. No claims are allowed.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571)-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Narayan K. Bhat

Examiner, Art Unit 1634

/JD Schultz/

Supervisory Patent Examiner, Art Unit 1635